BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants: Osvaldo A. Flores *et al.*

Application Number: 10/510,912

Attorney Docket Number: 21080P

Filing Date: October 8, 2004

Title of the Invention: Hepatitis C Assay Systems

Examiner: Zachariah Lucas

Art Unit: 1648

APPEAL BRIEF

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MERCK & CO., INC.

By _____ Date June 30, 2008

Melissa B. Wenk

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LIST OF CITED REFERENCES

International Publication WO 02/059321 (hereafter "De Francesco")

US Patent No. 6,297,003 (hereafter "Rice I")

International Publication WO 01/89364 (hereafter "Rice II")

US Patent No. 6,063,562 (hereafter "Melnick")

US Publication No. 2004/0018529 (hereafter "Li")

US Patent 5,783,669 (hereafter "Hawkins")

REAL PARTY IN INTEREST

The real party in interest is Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

There are no pending related appeals and interferences.

JURISDICTIONAL STATEMENT

The Board has jurisdiction under 35 U.S.C. 134(a). The Examiner mailed a final rejection on November 30, 2007, setting a three month shortened statutory period for response. The time for responding to the final rejection expired on February 29, 2008. A Notice of Appeal was filed on February 29, 2008. The time for filing an Appeal Brief is two months after the filing of the Notice of Appeal. The time for filing an Appeal Brief expired on April 29, 2008. This Appeal Brief is being filed on June 30, 2008 concurrently with a request for a two month extension of time under Rule 136(a), thus extending the period of reply to June 29, 2008. Since June 29, 2008 was Sunday, this Appeal Brief is timely filed on June 30, 2008 (the first business day after the due date).

STATUS OF CLAIMS

The status of claims is as follows: (1) claims 1-18 and 22-27, 30 and 42 are canceled; (2) claims 21, 39-41 and 43 are allowed and (3) claims 19, 20, 28, 29 and 31-38 stand rejected. The rejection to claims 19, 20, 28, 29 and 31-38 is being appealed. The rejected claims (claims 19-20, 28-29 and 31-38) are provided in the Claims Appendix.

STATUS OF AMENDMENTS

Amendments to the claims were made in response to the final rejection mailed February 29, 2008. The Examiner has entered those amendments as stated in the Advisory Action mailed March 26, 2008.

SUMMARY OF CLAIMED SUBJECT MATTER THAT HAS BEEN REJECTED

The present invention is directed to chimeric HCV replicons. An HCV replicon is an RNA molecule able to autonomously replicate in a cultured cell and produce detectable levels of one or more HCV proteins. The HCV replicon expresses the HCV derived components of the replication machinery and contains cis-elements required for replication in a cultured cell. An HCV replicon encodes for a number of HCV non-structural polypeptides including the polyprotein NS3-NS4A-NS4B-NS5A-NS5B (also referred to as NS3-NS5B). HCV replicons may also encode for the non-structural protein NS2 in the polyprotein (also referred to as NS2-NS5B). Additionally, the HCV replicon contains a suitable 5'-UTR-partial core (PC) region and 3' UTR. (see page 9, lines 12-30 of the instant specification)

Independent claim 19 is directed to a chimeric HCV replicon that has a 3' UTR from HCV-1a. Chimeric HCV replicons contain HCV regions from at least two different HCV strains. One or more different regions of a functional HCV replicon can be replaced with an HCV region from a different strain, including HCV obtained from a patient infected with the virus to obtain a chimeric replicon. (see the paragraph spanning pages 12-13 of the instant specification) Claims 28-29 depend from claim 19 and further specify that the chimeric replicon comprise a beta-lactamase reporter (claim 28) or that it does not contain a sequence coding for resistance to an agent that inhibits cell growth (claim 29).

Claim 20 depends from claim 19 and further distinguishes the claimed invention by providing that at least one of the regions in the chimeric replicon consists of a non-structural region from a clinical isolate of HCV. Claims 31-38 depend from claim 20 either directly or indirectly. They further specify the region of the replicon to be replaced by the region of the

clinical isolate (claims 31-32), the reporter system used in the replicon (claims 33-34 and 37-38) or the presence of non-naturally occurring restriction sites in the replicon (claims 35-36).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether claims19-20, 28, 29, 31-34, 37 and 38, directed to chimeric HCV replicons comprising at least two HCV regions that are from different strains wherein one of the regions is an HCV-1a 3' UTR and may consist of a non-structural region from a clinical isolate, are unpatentable under 35 U.S.C. § 103 based on De Francesco in view Rice I and Rice II and further in view of Melnick and Li.

II. Whether claims 35-36, directed to chimeric HCV replicons comprising an HCV-1a 3' UTR and a non-structural region from a clinical isolate with restriction sites not present in naturally occurring HCV, are unpatentable under 35 U.S.C. § 103 based on De Francesco in view Rice I and Rice II and further in view of Melnick, Li and Hawkins.

III. Whether claims 19-20, 28, 29, 31-34, 37 and 38, directed to chimeric HCV replicons, are unpatentable for nonstatutory obviousness-type double patenting over co-pending application Serial no. 10/543,633.

ARGUMENT

I. U.S.C. § 103 Rejection of Claims 19-20, 28, 29, 31-34, 37 and 38

Claims 19-20, 28-29, 31-34 and 37-38 have been rejected under 35 U.S.C. §103(a) as being obvious over De Francesco in view of Rice I and Rice II and further in view of Melnick and Li. Appellants respectfully disagree.

A. Claims not requiring inclusion of a portion of a clinical isolate

De Francesco teaches HCV replicons with adaptive mutations to enhance replicon activity. The replicon sequences disclosed are that of HCV con-1, a consensus HCV sequence. De Francesco does disclose that other naturally occurring HCV 3' UTRs can be used. Although the 3' UTR from HCV-1a is not specifically mentioned, it is a naturally occurring UTR as the Examiner points out. However, broad, generic disclosures are inadequate to establish obviousness as to a species. *See Ashland Oil*, 776 F.2d at 296-97, 227 U.S.P.Q. at 666-67; *In re Jones*, 958 F.2d 347, 349-50, 21 U.S.P.Q. 2d 1941, 1943 (Fed. Cir. 1992) (disclosure of a genus in a prior art reference does not in itself render a species of that genus obvious).

The Examiner contends that the present situation differs from the case cited *supra* in that here the claimed species was specifically named. Appellants respectfully disagree. The disclosures of De Francesco and Rice II simply recite that *any* naturally occurring UTR could be used. Appellants do not agree that this is tantamount to disclosing a specific species in the genus. Just by including a statement disclosing the universe of all UTRs, Appellants do not believe that one skilled in the art would be enabled to practice the present invention.

The Examiner relies on Rice I as specifically disclosing a number of HCV-1a 3' UTR sequences and thus distinguishing the present circumstances from those of the cited case *supra*. However, a closer look at the disclosure of Rice I reveals that this is not the case. While Rice I does disclose specific HCV 3'UTR sequences, they are not restricted to HCV-1a sequences, nor or HCV-1a singled out as better than the sequences of other strains. Of the 17 specific 3' UTR sequences recited (*i.e.*, SEQ ID NOS:1-4, 20-24, 28-31 and 33-36), only 5 are from HCV-1a (*i.e.*, SEQ ID NOS:20-24). The remaining sequences are derived from HCV-1b, HCV-3, HCV-4 and HCV-4a. (see col. 11, lines 20-57; col. 17, lines 55-62). Appellants believe that, while the genus disclosed in Rice I is smaller than that disclosed in De Francesco, it is a genus none the less. The disclosure is analogous to the disclosure of De Francesco where the 3' UTR of HCV-1a was not pointed to as being more advantageous than any other 3' UTR. As such, Appellants contend that there is no specific suggestion to use HCV-1a 3'UTR even when combining De Francesco and Rice I.

Additionally, the Examiner had stated that substitutions of HCV-1a 3'UTR into the replicons of De Francesco would have been obvious because "those of ordinary skill in the art would have been motivated to make such substitutions because the art indicates that the 3' UTRs of Rice are functional equivalents for the sequences provided in De Francesco" (see page 6, lines 2-4 of the Office Action mailed July 9, 2007). However, the Examiner had provided none of the art that describes the 3' UTRs of HCV con-1 and HCV-1a as equivalent. In response, the Examiner has clarified his position by stating that "the teachings of De Francesco [that naturally occurring HCV 3' UTRs and functional equivalents thereof can be used in replicons] indicate that the HCV 3'UTRs may act as functional equivalents of each other, and therefore provide

adequate basis to render the use of any known HCV 3' UTR obvious" (see page 4, first full paragraph in the Office Action mailed November 30, 2007). Appellants disagree.

De Francesco states that two types of 3'UTRs can be used - - namely naturally occurring HCV 3'UTRs and functional equivalents of naturally occurring HCV 3'UTRs (see page 10, lines 23-30 of De Francisco). This statement does *not* imply that all naturally occurring HCV 3'UTRs are functional equivalents of each other as the Examiner has characterizes. Accordingly, the Examiner must still cite art that describes the 3' UTRs of HCV con-1 and HCV-1a as equivalent. The rejection of a claim based on the Examiner's opinion, without additional evidence, is impermissible. *In re Zeidler*, 682 F.2d 961, 967 (CCPA 1982).

B. Claims requiring inclusion of a portion of a clinical isolate

The Examiner admits that neither De Francesco nor Rice I teach or suggest using HCV regions isolated from clinical isolates in the disclosed replicons. The Examiner cites to De Francesco as teaching that HCV replicons can contain 3'UTR sequences from different HCV subtypes or strains. The Examiner combines this teaching with the teaching from Rice II that HCV replicons can have portions (including non-structural polypeptides) from different HCV strains or subtypes. However, Rice II still does not teach or suggest using portions of HCV from clinical isolates. The Examiner contends that the teaching or suggestion of using portions of HCV clinical isolates in an HCV replicon can be inferred from Rice II. Appellants respectfully disagree.

In the Background Section of Rice II, it is stated that chronically infected individuals have changes in the virus population over time and that these changes may have

important consequence for disease (see page 7, 18-21 of Rice II). However, the disclosure goes on to highlight a hypervariable region of the E2 glycoprotein (an envelope glycoprotein). There is no mention of any other HCV protein (including any non-structural proteins such as NS5B) being particularly prone to mutation. This sole disclosure in the Background Section pertaining to viruses in infected patients is apparently the motivation for the Examiner to interpret the phase "other stains or subtypes" in Rice II as inferring clinical isolate sequences.

Appellants question that if such a meaning was contemplated by Rice II, why were terms such as "clinical isolate" or "patient sample" not used in description of their invention? Those terms are clearly the most commonly used and clear to those skilled in the art in conveying that concept. Appellants believe the Examiner is stretching the meaning of the description of the invention in Rice II in order to import the instantly disclosed invention when those skilled in the art would not have done so.

Rice II discloses that replicons can be used to screen for anti-viral compounds and should have "wild type" sequences. The Examiner interprets this to suggest use of clinical isolate sequences. However, throughout Rice II, the term wild type is consistently used to refer to a starting sequence *before* mutation. Any examples of altered sequences of HCV after replication in cell culture are referred to as adaptative *mutations* or *variants* (see, *e.g.*, page 62, lines 18-30 of Rice II). The Examiner is taking that one statement in Rice II with respect to wild type sequences and viewing it through the prism of the Appellants' disclosure to interpret it to mean clinical samples. Without the improper of use of hindsight, one of skill in the art would not have taken that statement in Rice II to mean clinical sample isolate sequences.

Even assuming *en arguendo* that the reference to "wild type" in Rice II does mean a clinical isolate sequence, Appellants still fail to see how such a statement would be interpreted by one skilled in the art as pertaining to the cited statements concerning sequences from different HCV subtypes or strains to arrive at the claimed chimeric replicons.

The Examiner also cites Melnick and Li as teaching the use of clinical isolate sequences. Melnick is directed to methods of predicting the identity of HIV protease mutants that emerge in response to drug treatment. Appellants note that throughout Melnick, clinical isolate sequences are referred to as "mutant" rather than "wild type" as in Rice II. The passage cited by the Examiner as having relevance to the instant application (*i.e.*, column 11) is directed to the use of their disclosed methods to evaluate the efficacy of a drug against various proteases, some of which can be mutant forms from clinical isolates.

Li is directed to methods of cloning genes encoding proteins involved in proteolytic cleavages and methods of finding protease inhibitors. The passage cited by the Examiner as having relevance to the instant application (*i.e.*, paragraph 9) is in the Background section of Li where identification of protease inhibitors are said to be important because a number of viruses use proteases in their life cycle. Li proposes that their disclosed methods can be adapted to screen clinical isolates of HIV for drug resistance.

Although neither Melnick nor Li are directed to HCV or the use of any methods using a replicon, the Examiner contends that Melnick and Li were cited as providing a general motivation in the art to develop drugs against pathogens which develop resistance to known drugs during the course of infection (see page 5, lines 10-14 of the Office Action mailed November 30, 2008). Appellants pointed out that just because drugs are desired against clinical

isolates of a pathogen or that resistance to drugs in target pathogenic populations change over time, it does not follow that others skilled in the art would solve the problem in the same manner as does the present invention. The Examiner believes that a mode for solving the problem was suggested by the teachings in the prior art that provides motivation and as such, no improper hindsight was used in making the rejection. Appellants respectfully disagree.

Appellants contend that the *motivation* cited by the Examiner is the product of the use of improper hindsight. The Examiner is viewing the disclosure in Rice II with respect to wild type sequences and using that as the motivation to combine the disclosures of Melnick and Li with De Francesco. Appellants contend that interpreting the disclosure of Rice II as motivation is in itself using hindsight. The meaning given to the cited statements in Rice II by Examiner (and used as motivation) is a product of first reading Appellants' disclosure. Thus, without the improper of use of hindsight, one of skill in the art would not have taken that statement in Rice II to mean clinical sample isolate sequences or seem the statements as motivation for combining the cited references.

Also, the Examiner contends that Appellants failed to consider the teachings of Rice II as providing a suggested solution to the problem identified in Melnick and Li (see page 2, fourth paragraph of the Advisory Action mailed on March 26, 2008). Rice II discloses that the sequences of viruses can evolve over time. However, their solution to this problem is to use their disclosed HCV assay system to study the evolving sequences and to probe the basis of drug resistance molecularly (see the paragraph spanning pages 44-55 of Rice). Thus the solution to the problem posed by Melnick and Li concerning drug resistant viruses is to use the assay of Rice

II to study what makes the altered strains resistant - - not making a chimeric virus containing sequences from clinical isolates.

In view of the foregoing, Appellants respectfully request withdrawal of the rejection under §103.

II. U.S.C. § 103 Rejection of Claims 35-36

Claims 35 and 36 have been rejected under 35 U.S.C. §103(a) as being anticipated by De Francesco in view of Rice I, Rice II, Melnick and Li in view of Hawkins. Appellants respectfully disagree.

Dependent claims 35 and 36 are directed to the chimeric HCV replicons of claim 20 that further have non-naturally occurring restriction sites in the replicon. As discussed *supra*, Appellants contend that De Francesco, Rice I, Rice II, Melnick and Li do not render claim 20 obvious. If the base claim from which a claim depends is not made obvious by the cited references, then the dependant claim is not obvious over those same references as well.

Hawkins is cited to show that modifications to nucleic acid sequences could be made without affecting the encoded amino acid sequence. Appellants contend that this does nothing to remedy the deficiencies of De Francesco, Rice I, Rice II, Melnick and Li.
In view of the foregoing, Appellants respectfully request withdrawal of the rejection under §103.

III. Nonstatutory Obviousness-Type Double Patenting Rejection of Claims 19-20, 28, 29, 31-34, 37, and 38

Claims 19-20, 28, 29, 31-34, 37, and 38 have been provisionally rejected for nonstatutory obviousness-type double patenting as being unpatentable over the claims of co-pending application Serial No. 10/543,633. Applicants respectfully disagree with the Examiner's characterization of the subject matter of the claims as being patentably indistinct.

Appellants contend that SEQ ID NOs:1 and 3 have a 3' UTR from HCV-1b. SEQ ID NO: 1 is a HCV NS3-NS4A-NS4B-NS5A-NS5B polyprotein based on HCV-BK. SEQ ID NO: 3 is an HCV replicon that was constructed by replacing the NS3 through 3'-UTR sequence of the HCV-con1 replicon with the corresponding region from HCV-BK. (see paragraphs 24 and 138 of US Patent Publication 2006/0228697). Thus, the claimed replicon has a 3'UTR region from BK which is HCV-1b. All of the currently pending claims in the instant specification require that the replicons have a 3'UTR from HCV-1a.

The Examiner further contends that SEQ ID NOs: 2 and 4 of application Serial No. 10/543,633 have a HCV-1a 3' UTR. Appellants will consider submitting a Terminal Disclaimer should claims in this application or application Serial No. 10/543,633 be deemed allowable.

In view of the foregoing, Applicants respectfully request withdrawal of the provisional double patenting rejection.

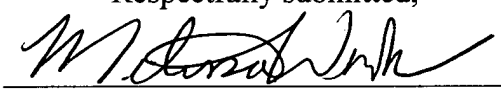
CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of and objections to claims 19-20, 28-29 and 31-38.

AUTHORIZATION

Please charge deposit account 13-2755 for fees due in connection with this Appeal Brief. Appellants petition a two month extension of time and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

Dated: June 30, 2008 By: 

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CLAIMS APPENDIX

19. A chimeric Hepatitis C Virus (HCV) replicon comprising at least two HCV regions, wherein the regions are from different HCV strains and wherein at least one of the regions is a HCV-1a 3' UTR.

20. The chimeric HCV replicon of claim 19, wherein at least one of said regions consists of a non-structural region from a clinical isolate of HCV.

28. The chimeric HCV replicon of claim 19, wherein said chimeric replicon comprises a beta-lactamase reporter.

29. The chimeric HCV replicon of claim 28, wherein said replicon does not contain a sequence coding for resistance to an agent that inhibits cell growth.

31. The chimeric HCV replicon of claim 20, wherein the non-structural region comprises a HCV polypeptide selected from the group consisting of NS2/3 protease, NS3 protease, NS3 helicase, and NS5B polymerase.

32. The chimeric HCV replicon of claim 31, wherein the HCV polypeptide is NS5B.

33. The chimeric HCV replicon of claim 20, wherein said chimeric replicon comprises a beta-lactamase reporter.

34. The chimeric HCV replicon of claim 33, wherein said replicon does not contain a sequence coding for resistance to an agent that inhibits cell growth.

35. The chimeric HCV replicon of claim 20, wherein said replicon comprises restriction sites not present in naturally occurring HCV that are located about 3' and about 5' from an HCV target region, wherein said restriction sites do not affect replicon activity.

36. The chimeric HCV replicon of claim 35, wherein said restriction sites are silent with respect to amino acid coding.

37. The chimeric HCV replicon of claim 35, wherein said chimeric replicon comprises a beta-lactamase reporter.

38. The chimeric HCV replicon of claim 37, wherein said replicon does not contain a sequence coding for resistance to an agent that inhibits cell growth.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None